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Pregnancy and diabetes

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University of Nebraska College of Medicine

Senior Thesis

1936

PREGNANCY AND DIABETES

G. Sherill McMillan

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PREFACE

In this paper, it has been my endeavor to list some of the important findings which have been published in relation to the problems which may arise, or which may accompany the situation, wherein a diabetic becomes pregnant, and the condition in which the pregnant woman shows signs of developing diabetes.

From the standpoint of statistics, it is evident that there are some 100,000 diabetic women of child-bearing age in the United States. The known pregnancy rate estimated from several series, is approximately ten per-cent: This indicates that the problem of pregnancy complicating diabetes is of increasing importance.

With the use of insulin, it is quite readily accepted that many more diabetic women who were previously sterile, are becoming pregnant. Under these conditions, the problem to the obstetrician in the care of such patients becomes more vital, this particularly in view of the diversity of opinion that still persists on this subject, and the gloomy prognosis which is frequently given.

The prognosis deals chiefly with the complications resulting in fetal mortality, for the investigations

of the cause and the means to prevent the occurrence of stillbirths in diabetics is the most important problem in pregnancy complicating diabetes.

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PREGNANCY AND DIABETES

A knowledge of the conditions and the possible complications which may arise in the problem of diabetes mellitus and pregnancy, is now more than ever of great importance, for pregnancy in the diabetic can no longer be considered a rare phenomenon.

The modern literature of to-day reveals the facts that the results of pregnancy in the diabetic have hitherto been disappointing, cases reported from most sources showing a persistently high fetal mortality in spite of the employment of insulin.

Bennewitz (60) in 1826 was apparently the first to record an instance of a pregnant diabetic. This was a woman who suffered from intense thirst and polyuria during three successive pregnancies. Bennewitz stated that the taste of the urine resembled beer but was much sweeter and that the urine contained two ounces of saccharine matter per pound. A second case was published by Lever in 1847.

In 1856, Blot (61) stated that sugar could be usually found in the urine of lactating women, but after it had

been demonstrated that the condition was a lactosuria, the belief gained ground that the existance of true diabetes was inconsistent with conception. This was first combated in 1882 by Matthews Duncan, who was able to find in the literature twenty-two cases in which pregnancy was complicated by diabetes, and he laid down the dictum, which recieved general acceptance, that such an association was extraordinarily serious.

It was not until 1909 that Whitbridge Williams (60) presented a summary of a comparatively large number of cases. In his series of sixty-six pregnancies in forty-three diabetics, twenty-seven per-cent of the mothers died during labor or the puerperium, generally from diabetic coma, and a further twenty-three per-cent succumbed during the succeeding two years.

In 1923, Joslin (20) stated that if a pregnant woman acquired diabetes the advice would be to allow the pregnancy to continue until contraindicated by inability to control the diabetes. This being the course he followed in 1914 and 1916.

If a diabetic becomes pregnant it is more serious.

In surveying diabetes and pregnancy in any era it can generally be assumed that diabetes may endanger both the

life of mother and child, even in spite of careful medical management. In considering the potentialities of maternal mortality it is found that in the preinsulin period Hirschfeld estimated this at fifty per-cent. Williams (58) in sixty-six cases reported that twenty-seven per-cent of the mothers died at the time of labor or within two weeks, while an additional twenty-three per-cent succumbed during the succeeding two years. Moreover about one-eighth of the pregnancies ended in abortion or premature labor and one-third of the children going to term were born dead. Ronsheim (45) in his works reports that maternal mortality before the days of insulin varied from fifteen per-cent to thirty per-cent during pregnancy, labor, and the puerperium with an additional ten to twenty per-cent dying within the year following of diabetes or tuberculosis. A much higher mortality was reported by Offergeld who in 1909 collected fifty-seven cases of which eighty per-cent died in coma during labor or the puerperium or within fourteen months thereafter.

Maternal mortality in contrast to the high fetal mortality has been low. In the combined eras it was five per-cent, in the preinsulin era, five-per-cent, and in the insulin era, five per-cent (51). The deaths in the pre-insulin era were all diabetic; the deaths in the insulin era were all obstetric. (51)

The course of pregnancy in the diabetic patient presented a gloomy picture prior to the introduction of insulin. Formerly when pregnancy occurred in a severely diabetic woman, the outlook for survival was poor for both the mother and the child. Wiener (54) reported thirty per-cent mortality during labor or immediately post partem, and twenty-one per-cent mortality during two and one-half years because of the increased severity of the disease following pregnancy. Some of the French authors (d'Offergeld, de Vincy) have found that fifty to fifty-five per-cent of diabetic women out of a hundred die during gestation, the puerperium or a few months later.

Fetal Mortality

In Joslins series of eighty-nine cases, 1898-1928, of these there were forty-two living children, fourteen still births, thirteen miscarriages and six therapeutic abortions. Both DeLee and Williams in older editions of their books state about sixty-six per-cent fetal mortality. In present insulin group only about sixty-three per-cent mortality. The still births at term are responsible for fifty per-cent of fetal deaths.

Intra uterine, intrapartum, and post partum deaths of infants of diabetic mothers have maintained a high rate. Priscilla White (51) has stated the problem well, "prevention of the death and decay of the overripe fetus of the diabetic mother is a challenge today to the obstetrician and research worker in the field of diabetes."

The obstetrical problem of delivering a live infant seems best solved by terminating the pregnancy at about the thirty-seventh week, in the majority of instances, by caesarian section. This has been done in the past two years for six of eight patients of Randall and Rynearson (43), and there have been no fetal deaths during intra-uterine life, during delivery, or post partum. Such an outcome necessarily is based on good cooperation between patient and physician in maintaining constant control of the diabetes throughout pregnancy.

Effect of diabetes upon the child is more or less interwoven with the effects upon the mother. Fetal mortality should embrace miscarriages, abortions, therapeutic abortions, and stillbirths, and some insist that deaths occurring within one to three days after delivery should be included. The high death rate is due to various causes, most important of which are acidosis and coma, hypoglycemia reactions, an overweight fetus, possible changes in the reproductive organs which may account for some of the miscarriages early in the pregnancy, and occasionally to diabetes itself.

The incidence of stillbirths in diabetics varies. In Kramers (24) records there were sixty stillbirths out of 238 pregnancies (twenty-five per-cent). The exact cause of death is not clear. Acidosis is the most likely explanation. However, there may be other contributory factors, æither toxic, metabolic, or endocrine, It is presumed that carelessness upon the part of the patient and failure to carry out the diet rigidly are responsible for this unfortunate condition. In some cases, stillbirths occur despite the cooperation of the patient and skillful medical care.

The fetus evidently dies late in the course of the pregnancy. Fetal heart sounds may be heard until the second or third week prior to the expected time of birth. Hypoglycemic shock in the newborn must be kept in mind. The

hyperplasia of the islands of Langerhans seen in some cases may be instrumental in producing hypoglycemic reactions after birth, unless the child is given carbohydrates. This may explain some of the deaths occurring shortly after delivery.

v. Noorden (33) relates that the infantile prognosis is very bad, with thirty per-cent missed abortions and fifty per-cent intra-uterine deaths (according to Seitz and Roland 62) and a high mortality. Accordingly, medium and severe diabetes has, in the great practice, long been an absolute indication for interruption, even during the inception of insulin therapy, although several cases with a normal course under strict diet or diet and insulin, have been reported.

Ronsheim (45) says that the effects upon the fetus are severe. He observed that fifty per-cent terminated in abortion, miscarriage, or premature birth. If the patient escapes these complications, fetal death in utero during the last few weeks of the pregnancy is always to be considered. In addition, the deaths from prematurity, monstrosity, and diabetes in early infancy raise this mortality to sixty-five per-cent or more. Here again, the proper treatment with diet and insulin, especially if it is instituted early, should result in a decided lowering of the fetal mortality, never-the-less, one must not lose

sight of the fact that the combination of diabetes with pregnancy is treacherous for both mother and child because numerous cases are encountered in which the presence of the disease is unsuspected until fetal death occurs, second, the glycosuria and the glycemia are so variable day by day that it becomes impossible to accurately judge the danger to the fetus, third, there seems to be no relationship between the severity of the diabetes and fetal mortality, last, the use of general anesthesia is apt to precipitate an attack of coma.

The investigation of the cause and the means to prevent the occurrence of still births in diabetes is the most important problem in pregnancy complicating diabetes. The incidence of still births has not been reduced adequately in the insulin era since seventeen per-cent of the pregnancies resulted in still births when even six per-cent is considered a high still birth rate. In patients under Whites (51) care, it has been reduced to one-third of the rate of the pre-insulin era and insulin era as a whole, but is still occurs twice as frequently in diabetics as it does in non-diabetics.

Mechanical, chemical, hormonal, or structural abnormalities may cause still births in diabetes. Maternal complications such as syphilis, heart disease, and anemias even not found in this series of the mechanical factors,

the size of the baby is the most important. Sixty-six per-cent or thirty-three of Whites babies, for whom they had data, weighed over eight pounds, compared with nine per-cent of one hundred babies reported by Carreno for a series which included one diabetic. The average weight for babies in the insulin era slightly exceeded the weight of the babies in the pre-insulin era. The size of babies of diabetic mothers is so striking that some clinicians call attention to the fact that a large baby may indicate maternal diabetes, and such mothers should be investigated for the disease. Obesity of the fetus in the diabetic may be due to over nutrition from hyperglycemia, lipemia, or to edema which is a direct result of the exogenous insulin. Possibility it is inherited obesity. Perhaps it is due to hyperactivity of the fetal or maternal pituitary gland. Permeability of the placenta to fat and pituitary like substances is known. Exogenous insulin is not the likely cause because the babies in the preinsulin era were large. The greatest growth of the embryo occurs in the last two months, at which time the blood sugar is generally normal. White (51) states that extreme hyperlipemia has not been observed in their own pregnancy cases. Thus insulin, fat, and sugar do not seem to be the probable causes of the overgrown fetus.

The mechanical difficulty of labor resulting from the delivery of the large baby, cannot be the most common cause of fetal death, though undoubtedly it increases the still-birth rate. Two-thirds of the fetuses were macerated or an incidence of one in seven in the insulin era compared with an incidence of one in eighty-three for non-diabetics reported by Dippel from the obstetric service of Johns Hopkins Hospital.

In 1909 Whitbridge Williams in his paper stated the fetal mortality, including abortions, was forth-one per-cent. Williams in 1930 suggested that these figures exaggerated the mortality, as probably some of the milder cases of diabetes in which pregnancy was uneventful did not appear in the literature. Never-the-less, it is obvious that before the discovery of insulin pregnancy in the diabetic was accompanied by grave danger for both mother and child.

Grahm (63) was the first in this country to record the case of a pregnant diabetic treated with insulin. By 1928 various papers appeared, the most comprehensive being that of Wilder and Parsons (56) who discussed the results of fifty-five pregnancies in fifty-one diabetics, including seven patients of their own. The maternal mortality was twelve per-cent and the fetal forth-seven per-cent. The 118 cases collected from the literature by Skipper (47) shows a maternal mortality of 9.3 per-cent

during pregnancy or the puerperium; diabetic coma, as in Williams' series being the chief cause of death. A further 3.4 per-cent of the mothers are said to have died within two years of delivery. The fetal mortality including abortions, stillbirths, and babies dying shortly after delivery, was 45.2 per-cent.

Causes of Fetal Death in The Diabetic

1. The control of the disease:

By far the most important cause of fetal death is neglect of the diabetes, especially during the latter months of pregnancy, and excluding all other possible factors this was responsible for fifty-six per-cent of the child fatalities in the collected cases and for fifty-three per-cent in the London Hospital series. In the badly treated diabetic the child is frequently born dead, often in a macerated condition, a few weeks before term, abortion in early pregnancy being relatively uncommon. The latter months of pregnancy are the most vital to the child, for inefficient control of the diabetes even in mild cases, is then particularly liable to be accompanied by a rising blood sugar and increasing ketosis in the mother; and such events are often followed by the death of the fetus in utero. It is because the importance of rigid control of the blood sugar has not been sufficiently realized that the fetal mortality in insulin-treated cases has been so high. Many early writers express belief that there is rather more likelihood of obtaining a living child in patients who develop diabetes during pregnancy than in those who were diabetic before conception. This is probably because diabetes complicating pregnancy is frequently mild and, the disease being of short duration, the mother is likely to be in good condition.

2. Excessive size of the fetus.

It has been known that the fetuses of diabetics tend to show excessive skeletal development and to be well supplied with subcutaneous fat. Yet, in spite of its manifest importance, this phenomenon has received little attention during recent years and is not alluded to in most modern text-books. But it is no exaggeration to state that the birth of a child of excessive size always suggests the advisability of investigating the mother for diabetes. In eighteen per-cent of the collected cases in which the weight is mentioned the child weighed ten pounds or more, the largest being a giant fetus of over seven kg. (47) Seven children in the London Hospital series weighed over ten pounds.

This overdevelopment is a not uncommon source of danger to the fetus and may cause its death from trauma sustained during difficult labor.

Bowen (9) has observed that overdevelopment of the fetus is apparently common in the diabetic mother. In his six cases born at term, three weighed ten pounds or over and one weighed nine pounds. Ehrenfest and Lobbe (63) cite a case reported by Dubreine and Anderodias in which the child of a diabetic woman weighed 5000 grams, although born one month prematurely, the islands of Langerhans were markedly hypertrophied as were those in the case of Gray

and Feemster, which died five days after birth, presumable of a hypoglycemia. Lesions were found in the pancreas of both mother and child in Ambard's case.

Why the fetus should be large in diabetes is a matter for conjecture, but it is tempting to correlate its abnormal amount of adipose tissue with maternal hyperglycemia. Thus the child tends to be fat, especially when the maternal disease has not been well controlled during pregnancy. In these circumstances the fetus is presented with a rich supply of glucose from the maternal blood stream, glucose being readily diffusible across the placenta from mother to child. (From Slemons, quoted by Skipper (47)). The excess sugar is presumably partly converted into fat and stored. It may be noted that high blood sugar values have been found in the umbilical cord in diabetics. In six of the hospital cases related by Skipper, the blood sugar in the umbilical vein, estimated immediately after birth, varied from 0.08 per-cent to 0.134 per-cent, and was in each instance slightly lower than in the mother. The ease with which glucose passes through the placenta was well shown in a case of Skipper's. The patient was purposely kept hyperglycemic during labor by the oral administration of glucose. Immediately after delivery the concentration of sugar both in the maternal capillary blood and in the umbilical vein was 0.25 per-cent.

3. Hydramnios.

Before insulin, hydramnios was said to complicate twenty-seven per-cent of cases and to have been a not infrequent cause of premature labor in the diabetic. Its incidence has diminished eleven per-cent and it does not now appear to be of great significance, although Voron and Gaucherard (63) were forced to puncture the membranes in their case because of symptoms of maternal distress. Hydramnios only occurs if the diabetes is neglected, and has been known to disappear on institution treatment with insulin. There was only one example of hydramnios in Skipper's (47) hospital cases, and this was in a woman who broke treatment continually. The presence of sugar, possibly derived from the fetal urine, has been reported several times in the liquor amnii of diabetics. Although the explanation is largely speculative the sugar content of the liquor in diabetes is possible the cause of the hydramnios, the raised osmotic tension in the amniotic cavity bringing about an inflow of fluid from the surrounding tissues. A further possibility is that the excess of liquor results from intra-uterine fetal diuresis consequent upon fetal hyperglycemia.

Kramer (24) says that regardless of the nature of this fluid, whether it be a secretion of the amniotic membrane or a urinary excretion from the fetus, it is an

accepted fact that an excessive amount of amniotic fluid is not infrequent in diabetics.

In the writings of White (51) the opinion is a little more conservative. "Hydramnios, which also endangers the life of the fetus is believed to occur in diabetes, and is held as a cause of fetal mortality. We have observed it but twice. This is suprising because the common causes of hydramnios, namely fetal deformities, large children, and maternal toxemias occur in diabetes. The origin may be chemical." Seven of the twenty-six cases collected by Graefe (64) were complicated by hydramnios. Graefe has also demonstrated an excess of glucose in the amniotic fluid in five out of ten diabetic pregnancies. Perhaps a better control of glycemia may have resulted in correction of this complication.

4. Congenital abnormalities.

Since Lecorche' (63) reported that two of his diabetics bore hydrocephalic children, it has been stated, although hitherto with little evidence, that congenital anomalies are common in the fetuses of diabetics (54). Congenital defects are mentioned in three per-cent of the collected cases and include a case of meningocele resulting in operative cure (38), a case of bilateral double-ureter and pelvis (18), and two instances of congenital morbus cordis (63). It is of interest that Rosenberg (63) in preinsulin

days also recorded that the child of a diabetic died with congenital heart disease and that the infant of a case in The London Hospital series apparently succumbed from this condition. A previous pregnancy of London Hospital series resulted in the birth of a monster. Although the number of cases is too small to allow definite conclusions to be drawn, there would certainly seem to be an unusual tendency for the children of diabetics to show congenital abnormalities, and that these constitute a small but quite definite factor in the fetal mortality.

5. Fetal hypoglycemia.

Skipper (47) reports that hypertrophy of the Islands of Langerhans of fetuses born of diabetics has been observed on five occasions and is probably to be regarded as a compensatory reaction of the fetal pancreas in response to an excess of glucose in the placental circulation. Thus, in each case in which this histological change was found, the maternal blood sugar had not been well controlled during pregnancy. As the hypertrophic islands would be expected to secrete an abnormally large amount of insulin, it has been suggested that the child of a badly treated diabetic, if born alive, is in danger of succumbing from hypoglycemia developing after birth. In Gray and Freemster's case the child's blood sugar three days after birth, was 0.067 per-cent. The child died on the fourth day with a peculiar

pasty color, but in addition to hypertrophic islands of Langerhans autopsy revealed other lesions sufficient to have caused death. Although the blood sugar in the child cited by Nevinny and Schretter (63) was 0.052 per-cent at birth, it later rose to 0.172 per-cent and death occurred from congenital morbus cordis. There is no evidence in the other cases that death was due to hypoglycemia. In another case the child's blood sugar ten hours after birth was only 0.045 per-cent yet no unusual symptoms were observed. Although in the diabetic, fetal death from hypoglycemia originating in this way seems very possible definite proof of its occurrence is thus lacking, and further observations are necessary. The fetal pancreas in two of Skippers cases showed hypertrophic changes in the Islands of Langerhans, but a report upon these was deferred by Skipper pending the collection of other material.

There is also the possibility of the intra-uterine death of the fetus from hypoglycemia during maternal insulin reactions, but again, there is no definite evidence that this has occurred. It is interesting that one certain case (63) stated that the fetal movements became very violent when she was hypoglycemic. Lambie's patient, however, noticed a cessation of fetal movements under like circumstances.

The following is a preliminary report from Randall and Ryneerson (43), of the treatment of an infant who had spontaneous hypoglycemia. The principals of treatment of

the condition are demonstrated by the following case.

"The mother first came to the clinic August 24, 1925 when she was seventeen years of age. No abnormalities were found. She returned November 3, 1925 complaining of the cardinal symptoms of diabetes mellitus of one month duration. The concentration of blood sugar then was 280 mg per 100 cc and her urine which had been negative on the previous visit, contained sugar, acetone and diacetic acid. She was instructed regarding diet, and the use of insulin. August 13, 1926 she was operated on by C. H. Mayo for acute appendicitis, the appendix and chronically infected gall bladder with stones were removed. In 1927, she became pregnant and her diabetes was controlled carefully during this pregnancy. May 30, 1928 however, she spontaneously gave birth to an infant of approximately thirty weeks gestation, the mothers condition was satisfactory, but the baby died. December 2, 1929, she was delivered at about thirty four weeks of a baby that died. September 27, 1930, a baby was born at thirty-four weeks, this infant was dead at birth. During each of these pregnancies Drs. Wilder and Mussey had exercised every known precaution to guarantee successful termination of the pregnancy.

When the patient became pregnant again, it was decided to perform a cesarian section late in pregnancy. In view of the accepted fact that infants of diabetic mothers are

likely to die in the last few weeks of pregnancy, it was decided to perform this operation at the thirty-fourth week of gestation. Dr. Wilder, impressed by the observations made during the previous pregnancies, decided if possible to determine whether spontaneous hypoglycemia did occur in the infant and to combat it by the administration of glucose.

It is not to be assumed that the infant was out of danger at the end of the first day. For the next two days, cyanosis would develop at times, and seemed to be helped by feedings.

The following table gives the infants record for the first day following caesarian section.

A. M.

8:22-Blood from cord-sugar 194 mg/100cc
 8:45- " " mother-sugar 280 mg/100 cc
 9:00-Baby in incubator: O chamber (O:50-55%)
 10:30-Babys blood sugar-43mg/100cc convulsive movements of head.
 11:30-first feeding-15cc mixture (lactic acid milk with 10% Corn syrup)
 11:45-Subcutaneous injection of 10cc of 10% soln. of glucose.
 12:00-Respirations irregular.

P. M.

1:00-Blood sugar-115 mg/100cc
 1:30-Second feeding 30cc of mixture.
 3:30-Blood sugar 118 mg/100cc:Third feeding-30cc mixture.
 3:45-Regurgitation: larynx obstructed-Cyanosis relieved by aspiration of tracheae.
 4:30-Respirations regular
 5:00-Sugar in urine, grade I
 5:30-Fourth feeding--20cc of mixture.
 7:30-Fifth feeding-20cc-Regurgitation with cyanosis.
 9:30-Blood sugar 105 mg/100cc: Apnea, Cyanosis.
 11:00-Rectal drip: 5cc-5% solution glucose.
 11:30-Feeding 5cc of mixture each two hours during night.

It may be postulated that the infant, having been part of a diabetic mother for so long a time, required a higher level of blood sugar than the infant of a normal mother. Premature infants whose reflexes are not fully developed, frequently have trouble with tracheal obstruction from aspirated mucous and cyanosis appears. This type of difficulty developed in the case here reported. Aspiration with a tracheal catheter when necessary, and inhalation of O and CO₂ when needed, are part of the management of any premature infant."

Ibrahim obtained no definite evidence of the presence of an active proteolytic enzyme in the pancreas of the human fetus till after the fourth month of intrauterine life. Banting and Best (5) assumed that the glycolytic enzyme would develop about the same time. They were able to prepare a very active antidiabetic extract from the pancreas of fetal calves of less than five months development, in experiments which were concerned with their early development of insulin.

Gray and Feemster (18) reported hypertrophy and hyperplasia of insular tissue in an infant four days old of a diabetic mother. They found about three times as many islets as noted in normal infants. Nothmann and Hermstein (65) recently described persistent hypoglycemia in an infant born of a diabetic mother, which necessitated

three hourly injections of glucose in order to maintain normal blood sugar, death resulting from bronchopneumonia on the third day. The pancreas weighed five grams, three times normal, and there was distinct hyperplasia of the islets. These observers worked on the theory that the increased sugar in the circulation of the mother on passing thru the placenta into the fetal blood stream produced hyperglycemia and caused an increased demand upon the fetal islet tissue.

Britton (65) made comparisons of fetal and maternal blood under various conditions. Large amounts of insulin administered to the mother sufficient to produce hypoglycemia affect the fetus but slightly, especially in late states of gestation, indicating that, as gestation advances, the fetus makes important adjustments in response to various emergency conditions which may be imposed upon the mother. Wollensen (65) also found that insulin given the mother reached the fetus. Brands experiments showed that the placenta of the rabbit in the last quarter of gestation is permeable to the Cl ion, urea, glucose, pentose, glycine and aloin, but impermeable to lactose and sacchrose. The human placenta is permeable to urea at the time of parturition. Transplacental exchanges occur only with substances of molecular weights lower than the disaccharides.

In 1923, Simons, Stulz and Aron (9) concluded that placenta was probably permeable to insulin and that the insulin from the fetus protected the mother. Aron later on however, by the use of insulin injections reached the opinion that insulin was not passed through the placenta

In Gordons (17) study of a large number of diabetic mothers, he noted that the diabetic condition in these mothers was improved from the second to the seventh month of their pregnancy. In order for the severe diabetic mother to metabolize the increased amount of carbohydrate ingested, it is necessary that there be more insulin present than the mother can supply. It is reasonable to assume that this increased supply of insulin is derived from the pancreas of the fetus, or that the fetus metabolizes the surplus carbohydrate with the insulin it produces. By reason of this fact there is a greater supply of carbohydrate to the fetus than normally. This would account very logically for the increased size of the fetus at term. Because of this increased supply of carbohydrate to the fetus or the increased demand on the part of the mother for insulin, there results a hypertrophy and hyperplasia of the pancreatic tissue.

As the fetus continues to grow in utero, the pancreas is able to secrete more and more insulin, and capable of metabolizing larger amounts of carbohydrate. As the supply

of carbohydrate is diminished in preparation to the increasing supply of insulin, relatively, the fetus begins to suffer a greater danger, that of hyperinsulinism. This is substantiated by the extremely low blood sugars reported to be present in the blood taken from the heart at post mortem examinations.

Gordon (17) in reviewing the literature says that very little has been written concerning the subject, Ronsheim in 1933 found a few cases in the literature where patients were improved during their pregnancies. Heilberg 1928, after studying the pancreas of infants born of diabetic mothers found that the islets were increased, he even counted the islets and found them to be increased in actual numbers. Dubrevil and Anderodias studied the dead fetus of a diabetic mother and found an increase in the number of islets. Gray and Feemster found that the pancreas of a child born of a diabetic mother contained approximately twenty-four times as much insular tissue as a normal pancreas. Feldman, Wiener and Skipper have found a similiar pathology. Skipper theorized that the hypertrophic islets would be expected to secrete an abnormal amount of insulin and they felt that the child of a badly treated diabetic mother if alive, is in danger of succumbing from hypoglycemia, developing after birth. Feldman also

found in the fetal pancreas of his case that there was a definite hypertrophy as well as edema and interstitial pancreatitis. Nevinng and Schretter, together with Shoman and Mathier, have made a study of the blood sugar of normal and abnormal mothers and babies, and they found that in the normal cases that the blood sugar in the infant was in the same range as found in adults. In the abnormal cases, the blood sugar usually became very low, especially after birth. Carlson and Drennan, as early as 1911, in a study of the group of cases took bitches who were pregnant and removed the pancreas. They found that in these dogs the diabetes was better during pregnancy and concluded that this was due to the increase insulin given by the fetal pancreas of the puppies in utero.

Kramer (24) writes that "the improvement of the diabetes is attributed by many to the added secretion from the fetal pancreas." If the presence of fetal insulin were so essential to the mother, would one not expect to increase the dose of insulin to supplement for the lack of the fetal secretion after delivery? Kramer states that this is not borne out clinically. If anything, the mother must be carefully watched, and it may be necessary to diminish promptly the insulin dosage in order to avoid severe hypoglycemic reactions.

White (51) thinks that although the passage of insulin through the placenta has been demonstrated by some, the production of hypoglycemia in the fetus does not seem probable and calls to attention that Britton injected large amounts of insulin, producing maternal hypoglycemia with little or no apparent effect upon the fetus, also Plias and Woods have shown that in a pregnant woman near term, starvation for fifty hours in the last month of pregnancy is frequently followed by hypoglycemia and onset of labor, without injury to the fetus. White is impressed that the report of Gray and Feemster and others suggesting that an endogenous hypoglycemia is a cause of fetal death is an interesting possibility. Better control of diabetes has certainly reduced the still birth rate. Pathological evidence in favor of this theory is striking but the normal fetal pancreas has large islands, and the newborn and premature infant relatively low blood sugar levels.

6. Congenital Diabetes.

Through out the entire world, there is a noted increase in the incidence of diabetes and an understanding of the hereditary aspects of the disease would be of great value from the prophylactic angle since the earlier a condition of hyperglycemia is diagnosed and proper precautionary measures instituted, the greater is the possibility for that particular individual to live his allotted span of life.

Wright (59) states that heredity has been recognized as an etiologic factor in diabetes mellitus since early in the 16th century, so although diabetes is commonly believed to be produced by a number of extraneous causes, it may also be included among the hereditary diseases which have been transmitted through many generations. According to Mendel's theory of heredity, there may be a passing of the germ plasm from one generation to another without a trait becoming dominant in the offspring until the proper mating or the proper environmental condition for its development are present.

Mackler and Fischer (28) state that it is generally accepted that diabetes mellitus is a familial or hereditary disorder of metabolism. In fact Pincus and White (41) have been able statistically to show that diabetes is inherited as a medelian recessive characteristic. Experimental proof of this fact has been brought forward by Cammidge who was able by mating strains of mice having a high fasting blood sugar with those having normal blood sugars, to transmit hyperglycemia to succeeding generations as a recessive quality. Cammidge suggested that in human beings the same blood sugar conditions might occur.

According to Joslin an hereditary and familial tendency to diabetes is present in 24.6 per-cent of all diabetics and in a slightly greater percentage of diabetic

children. It remains to be discussed whether any evidence that the children of women who are diabetic during pregnancy may be born with the disease or whether they are specially prone to develop it. Wolff alleged that ten per-cent of living babies born of diabetics contracted diabetes shortly after birth and succumbed within a few years, apparently basing his opinion upon an earlier paper by Offergeld. Reference to the cases collected by the latter author, however, make it clear and there was no justification for Wolff's statement. With the possible exception of a child which was said to have died at twenty-one months, with hydrocephalus, thirst, and polyuria, it is very doubtful, that any of the children in Offergeld's series had or developed diabetes. (47) Several showed glycosuria at birth, but this alone is insufficient evidence of diabetes, for the fetus may pass sugar in the urine after birth if its blood sugar was raised in utero owing to maternal hyperglycemia. The following are instances of alleged congenital diabetes, (taken from 47). In Morrison's case a new-born child was said to have died from diabetes, and the diabetic mother also succumbed. No further details given. Ambard et al described an intra and inter lobar fibrosis of the pancreas in the fetus of a diabetic. The child's urine contained 1.2 per-cent of sugar,

and death occurred in twenty-three hours, but the islands of Langerhans were said to be normal. Feldman's case is even less convincing. In addition to showing hypertrophy, the islands of the fetal pancreas were edematous, and an interstitial pancreatitis was described. Post mortem, the fetal urine was found to contain sugar. In view of the well-known difficulty in interpreting changes in the pancreas, it would be unwise to assume congenital diabetes in either of these cases. Moreover, it is not in favor of diabetes that the grossest lesions were stated to be in the glandular portion of the pancreas and not in the islands. Both Naunyn and Joslin wrote that they had never seen a congenital diabetic, and the former recognized no authentic case in the literature.

Kramer (24) writes that a hereditary tendency to diabetes is said to occur in from sixteen to thirty-five per-cent of the children. One may assume that this influence would be noticeable in the newborn child. Fortunately, this does not exist, as only two or three cases have been reported in which diabetes was discovered at birth or a few days after delivery.

Maddox and Scott (29) treat the subject by saying that while certain inheritable derangements such as color blindness, albinism, alkaptonuria, et cetera, fulfil

with precision all the mendelian requirements, irrespective of race or clime, many less clearly defined and less localized maladies are apparently dependent to a greater or less extent upon inherited factors and await further elucidation. Among these appear metabolic derangements, such as diabetes mellitus etc., all of which no doubt in time will receive, the searchlight of modern genetic knowledge and analysis full upon them.

Pincus and White (41) state that approximately fourteen per-cent of a group of relative of diabetics given routine blood sugar examinations and twentyfive per-cent of those given sugar tolerance tests had abnormally high blood sugar values when comparison is made with similar determinations made upon certain groups of normal healthy persons with no family history of diabetes incidence. Where they examined in various types of matings, the incidence of such 'hyperglycemic' persons among the offspring, the data suggested that such individuals may be taken as future diabetics, since the ratios of them in these matings are approximately proportional to the ratios of presumed unidentified genetically diabetic individuals called for by the Mendelian hypothesis advanced to explain the inheritance of diabetes.

While various observers estimate that heredity is responsible for at least twenty-three per-cent of all cases of diabetes mellitus. Labbe' (25) finds evidence

of heredity in thirty-five per-cent of the severe cases and in twenty per-cent of the mild cases.

It might be of interest to note here that in the studies of Kern (23) he confirmed the previously observed fact that diabetes and allergy seldom occur in the same patient, but only if on adding the qualifying phase (at the same time). For it is here shown for the first time that diabetics in their past medical histories have an even higher incidence of allergy than the community at large. Finally, there is revealed between allergy and diabetes a significant relationship in family incidence, hitherto unsuspected.

The conclusions reached by Maddox and Scott (29) in their works are as follows:- The proportion of members of a general diabetic population of 250 whose pedigrees had been collected because they had a history of the diabetes in their blood relatives, was thirty-four per-cent. This figure for Sydney is higher than most of those given for other centers and suggests a hereditary factor. The patients were all of the poorer classes. The character of diet did not alter much from case to case before treatment. There was no evidence of consanguineous matings among their parents. They have been unable to estimate environmental factors by comparing the incidence of diabetes in the poorer and more well to do sections. They find that the familial arrangement of affected individ-

uals in their pedigrees approximates somewhat to that governing the appearance of recessive conditions.

The gene for mild diabetes might be present in a recessive form in diabetic families, but it shows up as true diabetes only when aggravated by some factor such as over eating, obesity, infection, shock, worry et cetera. The incidence of a history of diabetes in the parents, sibs and children in a control series of non-diabetic individuals from the same social environment was ten and eight tenths per-cent. The gene or genes for diabetes do not, in their experience, display any linkage with those of color, sex, or other diseases. They can discover no correlation between the clinical type, severity or biochemical character of diabetes, except that on the whole "inherited" diabetes is of a slightly milder character than the sporadic disease. This does not exclude the possibility that different varieties of diabetes, each having a distinct pathological basis, may exist. It can only be inferred that at present genetic analysis gives no clues to the differentiation of such separate varieties. When the two groups of patients, those with and those without, affected blood relatives were compared, fertility was found not to differ in the two groups, nor was any difference noted in the proportion

of the sexes affected. Direct transmission was more frequent through the female in nineteen instances, as compared with fourteen directly transmitted by the male, whereas when the diabetes was transmitted by a carrier the female carriers numbered fourteen and the male carriers seven.

Joslin (21) summarizes the condition by saying that diabetes is hereditary but perhaps a fourth or a fifth of the citizens of the United States who have no tendency to it are capable of transmitting it and no policy toward diabetes should be adopted which does not take cognizance of this fact.

The average diabetic with onset of the disease in 1934 will live twenty years instead of less than five years as at the beginning of the century.

One diabetic should not marry another diabetic and have children, and if he marries a nondiabetic or a diabetic family half of the children theoretically should be diabetic. Therefore if a diabetic decides to marry, he should choose a non-diabetic in a non-diabetic family and then the children can be expected to be free from the disease, although they too would be hereditary carriers and should avoid union with other such carriers.

Pregnancy in a diabetic is far safer than heretofore. Cesarean sections are indicated for primiparae, because of the lessening of the strain of confinement and because the babies of diabetics tend to be very large, and because death of the fetus, from some causes as yet undertermined,

occasionally occurs in the last four weeks of pregnancy.

The problem of inheritance of the diabetic is indirect here rather than direct, for according to the present belief the potentiality for developing diabetes is inherited as a Mendelian recessive trait and the child cannot inherit the disease from one diabetic parent alone, but only two diabetics, a diabetic and a hereditary carrier or two hereditary carriers. The children of these diabetics, however, will all be hereditary carriers of the disease, based upon an incidence of 0.3% diabetes in the general population, it is estimated that already twenty-five per-cent of our population must be carriers of the disease.

Significance of The Glycosurias of Pregnancy

Sugar in some form has been found on routine examination of the urine in from four to thirteen and six tenths per-cent of pregnant women. It is quite generally held that the glycosuria is usually due to a low threshold which is common during pregnancy. Thus, in certain gravid women, although the blood sugar response to the ingestion of glucose is normal, sugar is found in the urine during the sugar-tolerance test or after an ordinary meal because the threshold is low. Apart from the excretion of sugar, carbohydrate metabolism appears to be undisturbed. This is the only variety of glycosuria of pregnancy to which the term renal should be applied. A large proportion of pregnant women who excrete sugar in the urine may, however, be demonstrated to have a lowered assimilation limit for carbohydrate, quite apart from diabetes mellitus. The fasting blood sugar is either normal or slightly raised, but these individuals, sometimes quite early in pregnancy, show a delay in the fall of the blood sugar after the oral administration of glucose, a flattened curve resulting. According to some authors it is the prolongation of the curve rather than the height to which the blood sugar rises which is abnormal. Others report definite hyperglycemia, the character, of the curve approximating to that of true diabetes. Pillman-Williams and Wills (63)

found hyperglycemia after 100 grams of oral glucose in eighty per-cent of pregnant women who had symptomless glycosuria upon an ordinary diet, and they concluded that the renal threshold was probably also lowered in all their cases. In Skippers (47) experiences hyperglycemia during pregnancy in non-diabetics was comparatively rare, but the 'plateau' type of curve was not uncommon and was practically always associated with a low renal threshold. In such cases the glycosuria is due to the latter and not to a hyperglycemia. Because patients with these anomalous curves tend to excrete sugar after meals, the condition has been almost universally referred to as 'alimentary glycosuria' of pregnancy, but this term is misleading and has led to considerable confusion, for also in ordinary renal glycosuria and in true diabetes sugar may be present in the urine after the taking of food.

Some observers hold that a woman may be 'diabetic' during pregnancy only, making a complete recovery after labor, but Skipper (47) states that he has never seen a permanent return of normal metabolism in any patients who showed a diabetic sugar tolerance curve when pregnant. Cases in which the diabetes was said to disappear after childbirth were probably not observed over a sufficiently lengthy period. The tolerance of the diabetic may improve greatly after delivery, and, with the rise of the threshold,

glycosuria frequently ceases. Yet, if the patient be placed upon an unlimited diet, the sugar-tolerance curve will sooner or later show the persistence of the treatment, the curve may be normal for a considerable time.

Diagnosis

In discussing the differential diagnosis, the following conditions which are associated with the excretion of sugar in the urine during pregnancy must be considered:

1. Glycosuria: a Renal glycosuria; b Impaired carbohydrate tolerance of pregnancy 'alimentary glycosuria'; c Diabetes mellitus.
2. Lactosuria.

1. Glycosuria. There has in the past been a tendency to assume too readily that a positive reduction of Fehlings solution obtained during pregnancy is harmless and may be ignored. Such an assumption is dangerous, for it has frequently led to the overlooking of the milder degrees of diabetes with disastrous results to the pregnancy. Undiagnosed diabetes is undoubtedly responsible for more still births than has been suspected, and the opinion is therefore expressed that glycosuria in the pregnant woman, like albuminuria, should always be investigated.

Regarding the clinical history, it must be remembered that mild thirst, polyuria, and especially pruritus vulvae, are not uncommon in the non-diabetic glycosurias, and, any pregnant woman may complain of them. A history of definite diabetic symptoms during the latter months of previous pregnancies, especially if these resulted in heavy children or in stillbirths, is strongly in favor of diabetes.

The sugar-tolerance test, which is of far greater value than single blood sugar estimations in distinguishing between the glycosurias of pregnancy should always be carried out whenever there is the slightest suspicion of diabetes. It is essential that the patient does not receive a diet restricted in carbohydrate for some days before the test is performed, for, if this precaution is not observed, a mild diabetic may give a normal blood sugar response leading to an error in diagnosis. In impaired carbohydrate tolerance of pregnancy, the blood sugar seldom rises as high as in true diabetes, rarely reaching 0.2 per-cent, and the fasting blood sugar is almost invariably below 0.12 per-cent.

2. Lactosuria. It is estimated (63), that lactosuria occurs in 3.5 per-cent of women during the last few weeks of pregnancy. Its renal incidence is probably much higher. It not uncommonly alternates with or accompanies glucose in any of the varieties of glycosuria. Lactosuria may be suspected when, in the absence of diabetic symptoms the urine contains a small quantity of sugar, usually under one per-cent, as term is approached.

Influence of Pregnancy on Diabetes

The question whether or not pregnancy alters the course of diabetes is still debated. In the literature one finds reports of gains in tolerance for carbohydrate and an equal number of reports of losses of tolerance for carbohydrates. White (51) states that a fairly general consensus of opinion is that a loss occurs in the first trimester, a status which is stationary in the second, and either a gain or less of tolerance in the third.

In the pregnant diabetic dog, Carlson and Drennan (64), were able to demonstrate a great gain in tolerance during pregnancy. That insulin circulates through the placenta of the mother is shown in the experiments of Pack and Barber (64). Insulin injected into the fetus of a goat was followed by the production of hypoglycemia in the mother. In the records of White (51) it is shown that half of the number with suitable records had milder diabetes during pregnancy than at any time before or after, but others have had more severe diabetes.

Skipper (47) noted changes in tolerance during eighteen pregnancies in seventeen women. These cases were all followed throughout pregnancy or from the earliest months. Alterations in the severity of the disease were estimated by comparing the diet and insulin prescribed at various periods, those during which the patients were stabilized

with normal blood-sugars being chosen for comparison whenever possible. During thirteen of these pregnancies the diabetes undoubtedly became worse, necessitating an increase in the dose of insulin. Skipper believes that infections and irregularities in diet and insulin probably contributed to the loss of tolerance sustained by four of these patients but, except for one case, the general course of events, especially the improvement during the puerperium, makes it unlikely that these factors were alone responsible.

"Immediately after delivery there is usually a very definite increase in carbohydrate tolerance, sometimes to such an extent that insulin can be temporarily lowered" (46). There are several cases reported in which insulin was dispensed with entirely for a short time. The reduced insulin requirement post partum is another good example of temporary improvement in tolerance due to relief of pancreatic overstrain. Macleod has emphasized the possibility of hypoglycemia following delivery as due to the passage of sugar from the blood to the breasts of lactation.

Bowen and Heilburn (9) state that when a diabetic becomes pregnant there is usually a decreased tolerance during this period. However some think that tolerance is considerably improved but from a collection of forty five case-reports by Bowen and Heilburn, the indications are that seventy per-cent seemed to show the equivalent of a

reduction of tolerance, that is, the insulin had to be increased or diet reduced.

Peckham (38) alleges that a gain in tolerance is actually to be expected as term is approached. There is no justification for this statement, as there is no doubt that an increase in the severity of diabetes during pregnancy is much more common. There have been many attempts to prove that any increase in tolerance is due to the transference of insulin from fetus to mother, the fetal pancreas partially compensating for the diminished production of insulin by the diabetic mother. Thus the hypertrophy of the islands of Langerhans of fetuses born of diabetics has been interpreted by many as evidence of a compensatory process in this sense.

A gain in tolerance often occurs after child birth, particularly in severe diabetes, and was noted in nineteen of the thirty-three hospital cases going to term or near it. (Skipper 47) Following delivery, in cases treated with insulin, the blood sugar is usually low, symptoms of hypoglycemia necessitating a reduction in the dose of insulin being extremely common. Insulin reactions, usually commencing during the first few days of the puerperium, occurred in seventeen of twenty-three of Skippers patients who were receiving insulin at delivery. Hypoglycemic coma was observed in three instances.

Wilder (15) states that tolerance is usually depressed in the first three or four months of pregnancy so that the patient taking a weighed diet of known compositions require larger doses of insulin than were needed before conception. He accounts for this on the basis of the ordinary "metabolic" abnormality of early pregnancy.

In Bowen's review of reported cases he showed that an increase insulin requirement was the general rule. In his five reported cases an actual increase was noted, but following parturition much less insulin was required. In Peckhams (38) series, in six patients who recieved insulin the requirement varied but little throughout pregnancy, but there was a tendency toward smaller insulin requirements. Improvement in carbohydrate tolerance as pregnancy advanced, with post partum hypoglycemia, was noted in two cases each by Hansen and Wilder et al.

Kramer (24) in discussing the effects of pregnancy upon diabetes states that one must consider the minor derangements of the carbohydrate metabolism in the pregnant non-diabetic patient. In such a condition the presence of sugar in the urine is not unusual. It may be transient or the glycosuria may persist. It is considered that a vast majority of these patients have a normal blood sugar. As a rule the glycosuria disappears with the termination of the pregnancy.

Opinion is divided concerning the influences of preg-

nancy upon one who is already diabetic. Some are convinced that the diabetic condition may improve. On the other hand, while it is true that there may be an improvement of the tolerance during certain months of the pregnancy, there may be a decided lowered tolerance for starches necessitating increased insulin dosage, in other stages of gestation.

The improvement of the diabetes is attributed by many to the added secretion from the fetal pancreas. If the presence of fetal insulin were so essential to the mother, one would expect that an increase in the dose of insulin would supplement for the lack of the fetal secretion after delivery. This is not borne out clinically. If anything, the mother must be carefully watched, and it may be necessary to diminish promptly the insulin dosage in order to avoid severe hypoglycemic reactions.

Kramer (24) thinks that it is quite possible that the explanation for any improvement may be the result of closer observation and better cooperation on the part of the patient, particularly when insulin is administered. The possibility of the fetus utilizing some of the available carbohydrates may also be mentioned.

Nalle (32) in writing on diabetes in pregnancy, subdivides the cases into three groups: I. Diabetics who

become pregnant. 2. The cases in which diabetes develops during pregnancy. 3. The pregnant women who show no signs of diabetes, but who after some catastrophe in pregnancy give evidence of having had a latent diabetes. Naturally the dangers are greater and the difficulties of handling are greater in diabetics who become pregnant than in the cases of those who develop diabetes during pregnancy. Ronsheim (45) makes this same division and comment. The danger to the child is probably greatest in the case of latent diabetes, for frequently harm is done to the child before the diabetes is suspected and before the administration of insulin.

The dangers of uncontrolled cases of pregnancy with diabetes are enumerated by Ronsheim: 1. Miscarriage. 2. Premature birth of a live child which may or may not live. 3. Death of the fetus in utero a few weeks before term. 4. Overdeveloped children-frequently necessitating section.

Complications and Effects of Diabetes on Pregnancy

Coma outranks all complications, and is usually due to carelessness. Acidosis predisposes to miscarriages and fetal deaths which is reasonable since the low CO₂ combining power of the mother might be expected to effect the normal interchange and metabolism in the placenta. The death of the fetus also predisposes to acidosis of the mother. Intercurrent infections are rare. Hydramnios is very common.

As has been pointed out, the babies born of diabetic mothers are usually large. Sherrill (46) is of the opinion that this may be attributable to hypofunction of other glands of internal secretion, the hypophysis and thyroid, since it is known that there is a hypofunction of other glandular structures in diabetes.

Kramer (24) points out that effects of diabetes upon the pregnancy may be manifested in the mother and in the child. Complications may appear in the form of miscarriages, abortions, therapeutic abortions, the necessity for induction of labor before term and hydramnios.

Miscarriage or abortions may result from the acidosis or may be due to some change, not clearly understood, in the reproductive organs that often exists in the diabetic patient.

Abortions and early miscarriages occur with relatively greater frequency in diabetic women after onset of the disease. White (51) states that twenty-two per-cent of their patients aborted in the pre-insulin era, compared with seventeen per-cent in the insulin era, and eleven per-cent in these same women prior to the onset of diabetes.

Premature expulsion of the fertilized ovum may be due to diabetic or non-diabetic causes. Among the diabetic causes must be considered a lethal factor in the egg, hypoglycemia, acidosis, deficiency diet, or lack of glycogen. The non-diabetic factor which, however, might secondarily be due to diabetes is excess of pituitary prolan A with consequent depression of the function of progestion. The studies of Senion (64) show that the fertilized ovum implants itself in that portion of the uterus which has the richest supply of glycogen. In uncontrolled diabetes, glycogen disposition is abnormal. Faulty nidation may result from depression of progestion.

White (51) is of the opinion that hypoglycemia, though capable of starting uterine contractions, probably is not an important factor, because abortions occurred even more frequently in the pre-insulin era. White also states that acidosis appears to be somewhat more harmful. However, only five of their fifteen patients who miscarried had acidosis, including one with chemical coma.

Treatment

Joslin (20) in 1923, advocated that treatment should be along the same line as treatment of diabetes apart from pregnancy and to bear in mind the sudden transitions which may occur in these individuals and the pains which must be taken to adapt the diet to their dietetic whim. He stated that there was no harm in keeping them undernourished until term, because thereby the mother would very likely be in a better condition and perhaps delivery easier because of the smaller baby. Joslin remarked at this time that insulin would doubtless save the lives of many pregnant women, but at that time experience with insulin was lacking.

Kramer (24) writes that the patient should be impressed with the necessity of cooperating faithfully, adhering to the diet and general care.

Frequent observations with routine urine and blood examinations should be made. Hyperglycemia should always be controlled.

The diet should be ample for the mother's needs, but is important to avoid overweight, having in mind the tendency to bear an overdeveloped fetus.

In later months, hospitalization is advisable, even if only for two or three days, so as to make thorough studies for acidosis and to standardize insulin dosage. Acidosis may exist without apparent signs or symptoms.

Coma may be precipitated without warning. It should be treated vigorously with insulin and, if there is no prompt response, the advisability of emptying the uterus should be considered.

Introduction of labor may be necessary in the late months of pregnancy if diabetic coma appears and is resistant to treatment. Labor may be induced before term in an attempt to deliver a live child when there is a history of previous stillbirths.

If the patient's condition is satisfactory, the natural delivery is preferable. There is no contraindication to a brief gas anesthesia if desired. Cesarean section has been advocated by some as the method of choice because it is a rapid means of delivery. It certainly is preferred when the patient requires assistance during labor. Spinal or gas anesthesia is far safer than either ether or chloroform which have a tendency to induce or aggravate acidosis.

In management of the postparturient period careful observation of insulin dosage and the blood sugar must be carried out. Hypoglycemic shock and coma are always

possible developments and sometimes it is difficult to differentiate between the two without proper blood studies.

When lactation sets in, the blood sugar may drop and the dose of insulin must be diminished promptly. This may be a temporary change. Later, the full dose of insulin may again be necessary.

The child should be carefully watched, especially for the first few days after birth, for the possibility of hypoglycemic shock.

In advising diabetics who desire children, the patients and family should be informed of the added risks, the likelihood of complications during pregnancy, plus the diminished chances of having a live child. However, there is always the possibility of going successfully to term if she is careful with her diet and if adequate insulin is administered. Treatment must be instituted early and maintained through out the pregnancy.

Sherrill (46) states that the treatment is little different than in treatment of regular diabetes. He is of the opinion that one should be cautioned against small insulin doses on the basis that the fetus will help provide the mother in the deficiency. There is much more danger in inadequate doses than large ones, if one expects a good per-cent of living babies. The diet must be liberal to provide for the demands of the fetus. It is a safe rule to give as much carbohydrate as the patient can tolerate,

with reasonable limits of sugar freedom; usually 125-150 grams is adequate. Special attention to mineral requirement.

The following is a case managed by Rathery, Sigwald, and Derot (44). The patient was a woman 28 years old. She had had diabetes since the age of 19 years. She had two carbuncles at the age of 19. Up to that time the only treatment for the diabetes consisted of diet but she had acetonuria on some occasions but in spite of this she married at the age of 22.

On her first admission to the hospital it was found that she had glycosuria without acetonuria. She was placed on a strict diet but the sugar did not disappear and in addition diacetic acid appeared in the urine. It was necessary to give her insulin. With a diet including 200 grams of potato, 40 grams of bread and 250 cc of milk it was necessary to administer 40 units of insulin daily. Two months later with this same diet and the 40 units of insulin it was found that she had a glycosuria of 21 grams daily with 0.58 acetone and 1.48 beta-oxybutyric acid.

In April 1929, with the same treatment, her urine contained 12 grams of sugar, 0.26 acetone and 0.62 of beta-oxybutyric acid. She had slight signs of intolerance. Her weight increased.

From April to October, 1929, she was given 15 units daily and no longer had signs of intolerance. Her urine contained 4.1 of sugar, 0.10 of acetone and 0.36 of beta-oxybutyric acid daily. The insulin was increased to 50 and then to 55 units in October. It was diminished to 30 in December.

In January, 1930 she had sugar 2.2, acetone 0.19 and beta-oxybutyric acid 0.19 daily.

She received the same treatment from December to June with 200 grams of potato and 40 grams of bread. Her weight remained at 53 kg. She sometimes had slight signs of intolerance toward noon after having received the injection of 30 units in the morning. The insulin was decreased to 20 and then to 10 units after which no insulin was given for 24 hours. She had 16 grams of sugar, 0.03 acetone and 0.15 beta-oxybutyric acid.

She was given 20 and later 30 units daily from July to December, 1930. Menstruation ceased after November 24 because she was pregnant.

On January 15, 1931, her treatment consisted of 30 units of insulin with a diet of 200 grams of potato and 40 grams of bread. The injection was given at 8:30 a.m. and then she ate a small amount of bread. She had malaise for three consecutive days about January 25. She went to sleep at noon on the first two days and did not awake

until 4 p.m. The attack was more severe on the third day and was accompanied by restlessness and by profuse serous and mucous expectoration. She had a tremor at 12:30 followed by asthenia with progressive somnolence and she remained in a comatose state until 4 p. m. She had contractures and trismus.

The following day the urinary reactions were negative. The insulin was then reduced to 20 units and her diet was increased by 20 grams of carbohydrates. This treatment was well supported and the pregnancy progressed normally.

Cizek (14) believes that every diabetic woman may become pregnant and give birth to a child without endangering her health, in so far as she is under constant medical supervision and adheres precisely to the proper diet. Cizek states that the indications for the interruption of pregnancy are as follows: 1. The impossibility for the woman to be under constant medical supervision. 2. Very severe forms of diabetes with high acidosis and defying insulin therapy. 3. Cases in which pregnancy markedly aggravates the diabetes and rapidly reduces tolerance.

Repeated pregnancies without injury to the health in diabetes are extremely rare. It is therefore advisable to avoid the danger of another pregnancy after two or three of them by operative sterilization or with the use of

contraceptives.

Some authors think that insulin fails too often in the case of coma, especially in pregnancy, when the pathogenesis of the acetone bodies is a quite peculiar one. Liebmann (27) states that only a very small number of cases have been treated systematically with insulin and diet throughout the entire pregnancy. In the majority, measures were only taken in the precomatose or comatose state. Umber claims that interruption is rendered unnecessary by a systematic combined treatment. Liebmann found this confirmed in four cases recently observed. That they were cases of genuine diabetes was shown not only by the fact that typical diabetic symptoms and a very marked glycosuria were present, but also by the fact that these symptoms were promptly influenced by diet and insulin, while pregnancy glycosuria, which is of a renal rather than an insular origin, is usually mild and refractory to such treatment. A precomatose condition appeared in one of Liebmann's cases, five days before admission to the hospital, upon a slight irregularity in the diet. In all the other cases, and also in this, aside from this accident, the course, delivery, and puerperium were free from severe complications for mother and child. The mothers were able to nurse their babies and felt well with a relatively full

diet and small doses of insulin. The babies showed a normal physiologic loss of weight, followed by a normal increase. As a rule, nursing should not be allowed in severe cases, on the one hand, because it is not good for the babies to be fed by a diseased organism, and on the other hand, because both diet and insulin dosage are rendered difficult.

Constant medical care, good will and will power on the part of the patient, and financial means are required for the carrying out of the cure; the delivery must by all means take place in one of the larger institutions, where internistic consultation can be obtained. Interruption is indicated whenever these conditions cannot be fulfilled. It is naturally always indicated in cases with severe complications, especially acidosis, or if the ketonuria keeps increasing. In the cases in which pregnancy is allowed to continue, the tolerance must be controlled very frequently, but the diet may be about five or ten calories per kg of body weight and $1\frac{1}{2}$ gm of proteins per kg of body weight higher than outside of pregnancy. Carbohydrate should be given in quantities sufficient to prevent the formation of acetone, especially of acetic acid. Enough insulin must be given to keep the urine free

from sugar with this diet.

The early nausea and vomiting of pregnancy can best be treated by hourly feeding and administration of insulin at three hour intervals. This of course may need to be supplemented by intravenous glucose.

Peckham (38) writes that the pregnant woman will tolerate a relatively high carbohydrate diet fairly well and in this way ketonuria may be controlled. The insulin dosage can be established by a study of the blood and urine sugar before and after each meal of the day. During the last part of pregnancy an improvement will probably be noted, the dosage of insulin may be diminished, and a careful watch should be kept for hypoglycemic reactions. At the time of labor the patient will be in good condition from a diabetic standpoint and no difficulty is to be anticipated. During the puerperium the diabetes may revert at once to its state before the pregnancy, but the improvement noted during the last few months may persist for some time. Lactation seems advisable in these patients.

"It is not desired in any way to make light of diabetes in the pregnant woman, as it is undoubtedly a serious complication. However, it is strongly felt that with careful supervision the average diabetic woman may relatively safely have her desired family and be left in no worse condition than before it."

Conclusions

Statistics show that the use of insulin has considerably lowered the maternal mortality of diabetics during pregnancy and the puerperium, but has led to no reduction in the fetal mortality.

The most important cause of fetal death is poor control of the maternal disease, particularly in the last months of gestation. Other causes are over-development of the fetus and congenital abnormalities. Hydramnios may be an occasional source of danger to the child. The occurrence of fatal hypoglycemia in the child after birth associated with hypertrophy of its islands of Langerhans has not yet been definitely proved.

Diabetics usually lose tolerance during the latter months of pregnancy. Although uncommon, an increase in tolerance may occur in the last half of gestation. There is no good evidence that this is due to the transference of insulin from fetus to mother. A gain in tolerance may be frequently observed after childbirth, the metabolic state of the patient often returning to that prior to conception. Hypoglycemia during the puerperium is almost

invariable in patients receiving insulin and may lead to hypoglycemic coma. It has been shown that lactation is not the chief cause of this hypoglycemia.

No evidence of congenital diabetes has been found. the child of a woman who is diabetic during her pregnancy is not specially liable to develop the disease. However, it is estimated that heredity plays an important factor.

As diabetes may commence during gestation, it is suggested that every pregnant woman whose urine contains sugar should be investigated as a possible diabetic.

During treatment constant supervision and rigid control of the blood sugar is of great importance. Only thus can a living child be obtained with reasonable certainty. Diabetics can now be safely brought through labor, but caesarean section may be necessary due to various fetal indications

Further pregnancies may be allowed in suitable cases if circumstances are favorable.

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